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Dated: October 22, 2007
Electronic Signature for Melissa L. Sistrunk: /Melissa L. Sistrunk/

Docket No.: AO-UTSC:791US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Mien-Chie Hung et al.

Application No.: 10/816,698 Confirmation No.: 1150

Filed: April 2, 2004 Art Unit: 1642

For: ANTITUMOR EFFECT OF MUTANT BIK Examiner: Goddard, Laura B.

REPLY BRIEF

MS Appeal Brief
Commissioner of Patents
Washington, D.C. 20231

Sir:

Appellants hereby submit a Reply Brief to the Board of Patent Appeals and Interferences in response to the Examiner's Answer dated August 22, 2007 ("the Answer").

The fee for filing this Reply Brief is $255.00. Appellants assert that an additional fee is not required, but if this is in error, please charge the Deposit Account 06-2375 under the reference number AO-UTSC:791US, from which the undersigned is allowed to withdraw.

REPLY BRIEF

Appellants address the Examiner's Answer herein. Appellants reiterate that the claimed invention generally concerns methods of inducing anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject by administering a mutant Bik polypeptide having an altered amino acid sequence, relative to SEQ ID NO:3, that comprises a substitution at least at Thr^{33} or Ser^{35}.

A. Summary of Arguments

Appellants address herein each of the specific rejections and rebuttal by the Examiner. However, Appellants assert that the claims are patentable, as summarized as follows:

- The claims on appeal have written description because they include both structural and functional limitations to the mutant Bik polypeptide, and there is correlation between the function and structure.
- The claims on appeal are enabled because it would not be undue experimentation to identify the effect of additional alterations to the mutant Bik polypeptide already having the substitution at Thr^{33} or Ser^{35} when the methods to test for the function of having anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity is disclosed and is routine in the art.

B. Issues under 35 U.S.C. § 112, first paragraph-Written Description

The rejected claims do not lack written description, because the specification provides enough detail about the alterations in the mutant Bik polypeptide, and the corresponding function, for the skilled artisan to recognize that Appellants had possession of the invention at the time of filing.

In particular, the Examiner maintains that the claimed subject matter does not meet the standards of *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), because the subject matter is allegedly claimed by the function of what

the gene does, rather than what the gene is, which requires a representative number of species. The Examiner considers the claimed subject matter to broadly be defined by an undefined structure—a mutant Bik polypeptide having any altered amino acid sequence, relative to SEQ ID NO:3 and having at least a mutation at Thr^{33} and Ser^{35} having particular activity, with a single representative, SEQ ID NO:9, having the sequence with the actual exemplary mutations (page 5 of the Answer).

However, Appellants' pending claims meet the standards set by *Lilly,* because the specification discloses the sequence of Bik polypeptide in SEQ ID NO:3, discloses an exemplary mutant Bik polypeptide in SEQ ID NO:9, discusses the generation of mutations in Bik, provides exemplary codons for the mutation in Table 1; and teaches biologically functional equivalents of mutant Bik. One of skill in the art would recognize that this disclosure was more than sufficient for the skilled artisan to recognize that the described guidance allowed the skilled artisan to employ the representative sequence in making the corresponding changes using the exemplary codons; the disclosure also teaches how to identify the altered polypeptides that comprise the desired function. The Examiner has failed to provide evidence why the skilled artisan would not reasonably conclude that the inventors had possession of the claimed invention (*Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)) and also failed to provide reasons why a person skilled in the art would not have recognized the description of the claims in view of the disclosure of the application as filed. *Interim Guidelines for the Examination of Patent Applications Under 35 U.S.C. 112, Paragraph 1,* Chisum on Patents, vol. 3, §7.04[1][c].

In the Examiner's Response to Argument (page 12 of the Answer), the Examiner considers Appellants' arguments to be unpersuasive by alleging that the specification and the claims lack identification of the critical structure required for the genus of mutant Bik polypeptides for functioning in inducing pro-apoptotic activity, anti-cell proliferation activity,

or anti-tumor activity. However, this is an inaccurate assessment of the claimed subject matter, because Appellants disclose that critical structures are the alterations at Thr^{33} or Ser^{35}, and although there may be additional alterations, as encompassed by the claims, the specific alterations at Thr^{33} and Ser^{35} are certainly necessary and disclosed as such. Appellants also provide the structure of SEQ ID NO:3 as a reference of a Bik polypeptide and provide the codon structure of exemplary alterations in Table 1. Therefore, Appellants respectfully assert that to characterize the claimed subject matter as lacking critical structure is a misrepresentation.

The Examiner also states in the Response to Argument (page 13 of the Answer) that Appellants misapply the written description requirement standard in *Lilly*. Appellants had argued that claim 12 recites SEQ ID NO:3 as being a relative sequence and that substitutions at Thr^{33} or Ser^{35} were sufficient to meet the standard in *Lilly* for providing structure. The Examiner found this unpersuasive because Lilly requires a precise definition structure and Appellants' disclosure of the mutant Bik polypeptide having any mutations relative to SEQ ID NO:3 allegedly fail to provide identifying structural features common to members of the genus. However, Appellants assert that they have met the standards in *Lilly* because they have provided a very particular reference sequence as a structural feature common to the genus, they have provided two specific alterations of the sequence as structural features that are common to the genus, and they have provided the well-known sequence of all of the 20 common amino acid codons that may be selected for the alterations in the reference sequence common to the genus. Therefore, Appellants have met the standards set in *Lilly*.

The Examiner also maintains that the claimed subject matter does not meet the standards of *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002), which sets forth the standard that the written description requirement can be met by disclosing sufficiently detailed and identifying characteristics when applied with a

disclosed correlation between function and structure (page 6 of the Answer). However, Appellants' claimed subject matter encompasses specific mutations at amino acids Thr^{33} or Ser^{35} that allow the polypeptide to induce anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity, so there was provided a disclosed correlation between function and structure, pursuant to the standards set in *Enzo*. The remainder of the mutant Bik polypeptide other than these sites finds guidance in the specification in reference sequence SEQ ID NO:3 and in Table 1, which provides codons for all standard amino acids.

On page 15 of the Answer, the Examiner rebuts Appellants arguments by arguing that the claims and specification do not teach the amino acids critical to the function of the polypeptide having anti-tumor activity, *etc*. In contrast, this is exactly what the claimed subject matter and the specification teach by disclosing alteration of Thr^{33} or Ser^{35} as the amino acid (alterations) that are critical to the activity. It is not necessary to teach other amino acids as being critical to the activity, or not, because the critical ones have already been disclosed. There may certainly be additional alterations, though, and the skilled artisan is guided as to the reference sequence for the additional amino acids that could be altered and the exact codon sequence needed for the alteration.

In the rebuttal, the Examiner finds unpersuasive Appellants' arguments that a representative number of mutant Bik polypeptides have been provided in the specification. The Examiner considers it insufficient that the specification provides broad definitions for the mutant Bik polypeptide yet acknowledges that Appellants have provided a representative sequence both with and without the claimed alterations for Thr^{33} and Ser^{35}, the amino acids critical to the claimed invention. In contrast, Appellants have provided written description under any guidelines by describing the critical amino acid alterations, providing structural and functional correlation of these particular amino acid alterations, and providing exemplary reference sequence and exemplary codons for alterations for the claimed subject matter.

Therefore, Appellants have met the written description guidelines in the pending claims, and respectfully request reversal of the rejection by the Board.

C. Issues under 35 U.S.C. § 112, first paragraph-Enablement

The appealed claims contain subject matter that was described so that a skilled artisan can make and use the invention, in contrast to the Examiner's allegations.

In particular, the Examiner alleges that one of skill in the art cannot extrapolate the specification's disclosure to enable the claims because the genus of mutant Bik polypeptides is too broadly drawn by encompassing mutant Bik polypeptides having any altered amino acid sequence, relative to SEQ ID NO:3, that comprises a substitution at least at Thr^{33} and Ser^{35}. The Examiner further states that the specification does not provide examples for predictably inducing anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity *in vivo*.

The Examiner reiterates that the cited references of Mathai *et al.* (2005; "Mathai"); Azar *et al.* (2000; "Azar"); and Bowie *et al.* (1990; "Bowie") cast doubt on the predictability of the claimed invention. For example, the Examiner suggests the following: (1) Mathai teaches that the mutant Bik would need to be located internally or it could not predictably induce apoptosis; (2) Azar teaches that the mutant form might elicit an immune response against the polypeptide, thereby rendering it ineffective; and (3) Bowie teaches that the three-dimensional structure of a protein is critical to its function. Although Appellants previously argued that the skilled artisan is aware of such routine issues and how to address them with well-known techniques, the Examiner found this unpersuasive because the Examiner circuitously argues that the references are supportive that the invention is unpredictable. In effect, the Examiner disagrees with Appellants that any experimentation to induce anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity *in vivo* is routine; the Examiner considers that the specification provides insufficient guidance because there is no

teaching for structural features common to the genus of mutant Bik polypeptides and there is no guidance for using the polypeptides as claimed.

The claimed invention already provides the important and very specific alterations in mutant Bik, so the question is whether or not additional alterations would allow the mutant Bik polypeptide to retain anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity. Is it undue experimentation to test if other alterations in mutant Bik affect this activity? The answer is no---Appellants have disclosed the critical alterations, provided a representative sequence, provided exemplary alterations, and demonstrated how to test for the activity. To practice the claimed invention may require some experimentation, but Appellants have sufficiently disclosed the information needed for the skilled artisan to make and use the invention. "The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). According to *Wands*, Appellants have certainly provided a reasonable amount of guidance by disclosing the critical amino acids, other amino acids that may be altered, and methods of testing them.

The Examiner also notes that the claimed invention is not directed to routine characterization of drugs but to inducing anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity *in vivo*. However, the specification provides guidance for multiple routes of administration of mutant Bik polypeptides and pharmaceutically acceptable excipients for the polypeptides.

Appellants reiterate that the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970), and guidance is not necessary to those skilled in the art, particularly when it is well-

recognized that the skill in the art of molecular biology is quite high (*Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986). Appellants have provided sufficient detail by providing an exemplary mutant Bik polypeptide having structural and functional correlation; an exemplary reference sequence for the polypeptide sequence outside of the mutations at Thr^{33} and Ser^{35}; exemplary codons for particular amino acids for the polypeptide sequence outside of the mutations at Thr^{33} and Ser^{35}; exemplary administration routes; and description of delivery and treatment protocols for utilizing the mutant Bik polypeptides.

Therefore, it would not be undue experimentation to make and use the invention, and Appellants respectfully request reversal of the rejections by the Board.

II. CONCLUSION

Appellants have provided arguments that overcome the pending rejections. Appellants respectfully submit that the Office Action's conclusions that the claims should be rejected are unwarranted. It is therefore requested that the Board overturn the Action's rejections.

Dated: October 22, 2007

Respectfully submitted,

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